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Observation of hyperpositive non-linear effect in catalytic asymmetric organozinc additions to aldehydes.[‡]

Yannick Geiger,^[a] Thierry Achard,^[a] Aline Maisse-François^[a] and Stéphane Bellemin-Laponnaz^{*[a]}

Abstract: Asymmetric amplification is a phenomenon that is believed to play a key role in the emergence of homochirality in life. In asymmetric catalysis, theoretical and experimental models have been investigated to provide an understanding of how chiral amplification is possible, in particular based on non-linear effects. Interestingly, it has been proposed a quarter century ago that chiral catalysts, when not enantiopure might even be more enantioselective than their enantiopure counterparts.

We show here that such hyperpositive non-linear effect in asymmetric catalysis is indeed possible. An in-depth study into the underlying mechanism was carried out and the scheme we derive differs from the previous proposed models.

Keywords: asymmetric catalysis, non-linear effect, homogeneous catalysis, zinc chemistry

Introduction

Non-linearity between the enantiomeric excess of a product and of a chiral auxiliary in asymmetric synthesis or catalysis is the result of interactions between the two enantiomers of the chiral auxiliary (i.e. diastereomeric perturbations).^{1–6} A non-linear effect that gives an asymmetric amplification (positive non-linear effect, (+)-NLE) is believed to play a key role in the emergence of biological chirality.⁷ In addition, understanding these non-linear effects is of great importance for asymmetric catalysis; it allows to clarify the mechanism and the nature of the species that are involved in the catalytic cycle.

Since the first comprehensive studies on asymmetric synthesis using scalemic chiral catalysts by Kagan and collaborators in 1986, several models have been proposed and verified by mathematical argumentation.⁸ In particular, Kagan proposed a model where the formation of catalytic species involving the combination of several chiral ligands is inducing the non-linearity: the model is based on a metal M bearing *n* ligands and thus is called ML_{*n*} model.¹ All these ML_{*n*} complexes, which are homo- or hetero-chiral species – depending on the enantiomers that are present around the metal – will then react simultaneously to give the product. Interestingly, it has been proposed for the ML₃ model that chiral catalysts, when not enantiopure, may be more enantioselective than their enantiopure counterparts, though such a case has never been observed experimentally until very recently.⁹

We discuss here the first example of such hyperpositive non-linear effect, which was observed while studying the addition of dialkylzinc reagents to aromatic aldehyde substrates with partially resolved chiral *N*-benzylephedrine ligands. A rationalization of the effect was possible by studying the concentration, temperature and aggregation effect on the catalyst. The reaction scope was also studied using various *para*-substituted substrates with electron-donating and electron-attracting groups. Overall, our results point toward a two-component catalysis, where a mononuclear catalyst is in equilibrium with a dinuclear catalyst, both systems being in competition to give the chiral product.

Materials and Methods

All reagents were purchased from commercial chemical suppliers and used without further purification, except for liquid benzaldehyde substrates that were distilled and stored under argon over 4 Å molecular sieves prior to use. (1*R*,2*S*)-*N*-benzylephedrine was prepared according to a literature procedure.¹⁰ The ligand ee was adjusted by preparing appropriate mixtures of the (1*R*,2*S*)- and (1*S*,2*R*)-enantiomers. Enantiomeric excesses were determined on a Varian 3900 gas chromatograph equipped with a CP-8400 autosampler and a Chiraldex G-TA capillary column (25 m long, 250 μm in diameter) with helium as carrier gas.

General procedure – *N*-benzylephedrine-catalysed addition of dialkylzinc to aromatic aldehyde. The procedure is identical to what has been published previously.⁹ In a N₂-filled glovebox, (1*R*,2*S*)-*N*-benzylephedrine (23.7 mg, 20 mol%, 92.6 μmol) and a magnetic stirring bar were placed in an oven-dried vial, which was then closed with a septum-containing screwcap. The vial was put out of the glovebox and a 15% ZnEt₂ solution in toluene (0.5 mL, 1.2 equiv., 560 μmol) was added via syringe; gas evolution occurred. After 10 min stirring, the mixture was cooled to 0 °C and benzaldehyde (47 μL, 1 equiv, 460 μmol) was added via syringe. The yellow solution was stirred overnight at 0 °C and turned colourless, then was quenched carefully with 3 M aqueous

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HCl in an ice-water bath under vigorous stirring. The organic phase was isolated, dried over Na₂SO₄ and analysed by chiral stationary phase GC.

ZnMe₂ was used as a 1.0 M solution in toluene (0.5 ml, 1.2 equiv., 500 μmol) with adapted ligand (21.3 mg, 20 mol%, 83.3 μmol) and benzaldehyde quantities (1 equiv., 420 μmol). Reaction media with ZnMe₂ stayed colorless and were let to stir for 4 days. The procedures were identical for the use of para-substituted benzaldehydes, except for those which are solid (CN, I, Br, Cl). Those were weighed and added into the vial inside of the glovebox, together with the ligand.

Results and Discussion

Alkylation of benzaldehyde

Because of the weak knowledge of NLEs with ephedrine-based ligands, we investigated the behaviour of N-benzyl ephedrine derivatives (NBE) in the zinc-catalysed alkylation of benzaldehyde. The reaction conditions have been fixed as displayed in Scheme 1. A key point to be made is the catalyst loading which was deliberately fixed at 20 mol%, thus promoting potential catalyst aggregation. The reaction temperature was fixed at 0 °C to minimize the achiral background reaction¹¹ and the formation of benzyl alcohol as side-product.¹²

SCHEME 1. Enantioselective addition of dimethyl- or diethyl-zinc to benzaldehyde, catalysed by chiral (-)-N-Benzylephedrine (NBE).

Figure 1 (a) displays the correlation between the enantiomeric excess of the product (ee_P) and the enantiomeric excess of the ligand (ee_L) with diethylzinc as reagent (red triangles). When the enantiopure ligand was used, the product was isolated in 76% ee . Interestingly, variation of ee_L lead to a very strong (+)-NLE: ee_P stays at high level down to an ee_L of only 3%, which is an unprecedented strong amplification in a non-autocatalysed reaction. Even more interesting is the shape of the curve: starting at 76% ee_P with the enantiopure ligand, the enantiomeric excess of the product ee_P increased up to 81% in the presence of (-)-NBE ligand of only 10% ee . Thus, the scalemic, enantio-impure catalyst lead to a more stereoselective reaction than the enantiopure one: this is a case of hyperpositive non-linear effect.

An even more significant hyperpositive non-linear effect was observed with dimethylzinc as reagent. Figure 1 (b) displays the result of our investigations (red triangles). While the enantiopure NBE induced a very low enantioselectivity of only 16%, the progressive decrease of ee_L lead to a seemingly exponential growth of the ee_P , with a maximum of 53% in presence of only 5% ligand ee .

FIGURE 1. Red triangles: optical purity of the product as a function of the ligand ee in the (-)-NBE-catalysed addition of ZnEt₂ (a) or ZnMe₂ (b) to benzaldehyde.⁹ Green squares: superimposition of ee_P as function of catalyst loading using either ZnEt₂ (a) or ZnMe₂ (b), which was previously converted to ee_P vs. simulated ligand ee (from Figure 2). Each point is the mean of three different experiments; the vertical bars depict standard deviations. The 2nd-order polynomial fits (dotted lines) serve as visual guidelines.

Mechanistic investigations

Given the importance of these experimental results, we decided to conduct in-depth investigations to determine the origin of such hyperpositive effect. The ML₃ model proposed by Kagan implies that the NLE curve can be hyperpositive in the upper half of the ligand ee scale and obviously, such a case cannot be considered here. Therefore, the ML₃ model is not applicable and we had to search for another model for this peculiar phenomenon.

A notable fact during our catalytic investigations is that upon addition of the dialkylzinc reagent, a precipitate was observed when the scalemic ligand was used, whereas the solution stayed clear with the enantiopure one. Further analyses of the hydrolysed precipitate obtained from 50% ee ligand samples gave the free ligand in its racemic form. This result suggests that the precipitate is most likely a *meso* aggregate of the zinc catalyst. Thus, the precipitation of an inactive heterochiral aggregate is in accordance with the emergence of a positive (+)-NLE, pushed by the presence of an active enantioenriched Zn complex in solution. We can reasonably apply here the “reservoir effect” model from Henri Kagan, which implies that part of the ligand is stored in a reservoir.¹

This implies also that decreasing the enantiomeric excess of the ligand would thus generate more heterochiral inactive aggregates and therefore less catalytically active species. Reducing the ee_L thus induces a decrease of the active catalyst concentration. We assumed that the observed hyperpositive non-linear effect could be linked to the effective catalyst concentration. Therefore, the enantioselective reaction was evaluated by varying

the catalyst loading of the enantiopure NBE ligand with diethylzinc (Figure 2 a) or dimethylzinc (Figure 2 b) as reagent. The results revealed that a decrease of the catalyst loading led to an increase of the enantiomeric excess of the product (from 76% to 84% ee with ZnEt_2 , and from 16% to 49% ee with ZnMe_2). Moreover, the shape of the two curves are identical with the one seen in our NLE investigations.

FIGURE 2. Optical purity of the product ee as a function of the catalyst loading in the addition of ZnEt_2 (a) or ZnMe_2 (b) to benzaldehyde, catalysed by enantiopure (-)-NBE.⁹ Each point is the mean of three different experiments; the vertical bars depict standard deviations. The 2nd-order polynomial fits (dotted lines) serve as visual guidelines.

Thus, it would seem possible to link the observed non-linear effects to the experiments from Figure 2. Indeed, if we assume that the heterochiral aggregate is fully precipitated, a catalytic system with e. g. 20 mol% catalyst loading of a ligand of 50% ee should be equivalent to a 10 mol% catalyst loading of enantiopure catalyst. Thus, we could correlate all data points from Figure 2 with a *virtual* enantiomeric excess if a scalemic ligand was used. The resulting graphs were superimposed with the hyperpositive NLE curves and are displayed in Figure 1 (green squares). In both cases, an excellent agreement was observed.

Based on these observations, it seems plausible that the catalytic system is composed of two independent catalysts that are in equilibrium and in competition: a monomeric species and a possible dimeric species that operate at a steady state. Alkylzinc

aminoalkoxides are known to form dimers (and even higher aggregates)^{13–16} which are at the origin of strong NLEs with the DAIB ligand in dialkylzinc additions.^{17–19} Assuming that the enantiomeric excess produced by the monomer catalyst (ee_m) is higher than with the dimer (ee_d), then decreasing the catalyst concentration leads to an increase of the overall ee_P as the equilibrium is shifted to the more enantioselective catalyst (i.e. monomeric species). In the same way, decreasing ee_L would have the same effect as it causes the lowering of the effective catalyst in solution and therefore gives rise to a hyperpositive non-linear effect.

Several additional experiments have been carried out to support this hypothesis.⁹ These experiments include the investigation of the impact of the reaction temperature on the ee_P, where an unusual inverse temperature dependence was observed. Indeed, the product ee_P increases with the reaction temperature, consistent with a monomer/dimer-equilibrium shifted towards the monomer at higher temperature. Additionally, ¹H DOSY NMR experiments were conducted to evaluate the degree of aggregation of the catalysts as function of the temperature. Finally, Visual Time-Normalised Analyses (VTNA) of kinetic profiles resulted in an unusual U-shaped catalyst order vs. catalyst loading plot, which was found to be consistent with a model in which both monomer and homochiral dimer catalyse simultaneously.

Proposed model

A mechanism that is coherent with the experimental investigations is displayed in Figure 3. It describes a catalytic system that operates with both a monomeric catalyst and a dimeric catalyst that operate at a steady state. If we assume that the enantiomeric excess produced by the monomer catalyst is higher than with the dimer ($ee_m > ee_d$), then decreasing the ee of the ligand induces a lower effective concentration of catalyst and therefore the equilibrium between monomer and dimer is shifting toward the more enantioselective monomeric species, which induces an increase of the overall product ee. This mechanistic proposal stands in contrast to the Noyori model for DAIB-catalysed dialkylzinc additions, which excludes the participation of dimers in the catalytic step.^{17–19}

FIGURE 3. Proposed enantiodivergent model for the NBE-catalyzed addition of dialkylzinc to benzaldehyde which explains the hyperpositive non-linear effect.

Substrate screening

As for now, there is a lack of information about the structure of the dimeric catalyst and how it catalyses the reaction. One way to obtain such information is to study the catalytic reaction with substrates that differ in their electronic or steric properties. Upon a change in the substrate, the monomeric and dimeric catalytic cycles may react differently: the reaction rate, enantioselectivity and affinity of the catalyst for the substrate – or for the product – may vary to different extents for both catalysts. This has been exploited for example by Noyori and collaborators in the case of DAIB-catalysed ZnMe_2 reactions, where they built Hammett plots using enantiopure and racemic (-)-DAIB.²⁰ As the plots turned out to be linear and identical, the authors concluded that in both cases the reaction was catalysed by an identical species. Since catalysis by homochiral dimeric $[\text{DAIB-ZnMe}]_2$ had been ruled out, they deduced that the catalytic species was a monomeric zinc complex, and catalysis by heterochiral dimers could also be excluded.

This led us to investigate several *para*-substituted benzaldehydes and study the influence of the electronic effects on the substrate. Substitution in *para* position was chosen to avoid any steric influence of the substituent onto the reaction mechanism. We performed a series of catalytic runs using either enantiopure or 20% ee_L (-)-NBE. The results are shown in Figure 4 (a) for ZnMe_2 and Figure 4 (b) for ZnEt_2 as reagent (for conversions, see Figure S1 and Table S1; for the data from Figure 4 see Tables S2 and S3). With ZnMe_2 , all substrates showed a hyperpositive non-linear relationship (i. e. ee_P from scalemic ligand is higher than from the enantiopure one), except those bearing an -OCF₃ or -SF₅ substituent. The ee_P difference between scalemic and enantiopure ligand (Δee_P) lies mostly between 18 and 25% (details can be found in the Supporting Information). With the scalemic ligand, ee_P increases when going from electron-donating ($\sigma_P < 0$) to neutral substituents ($\sigma_P \approx 0$), then reaches a plateau of ca. 40–45% ee_P. The enantiopure ligand roughly follows the same trend. -OMe, -OCF₃ and -SF₅ stand out as exceptions: they show overall lower ee_P than observed in the global trend; the ee_P yielded from enantiopure *para*-OMe-benzaldehyde even broke down to almost 0%.

Using ZnEt_2 as the dialkylzinc reagent leads to overall high ee_P values of ca. 70–80%, with both scalemic and enantiopure (-)-NBE (Figure 4 b). This leads to small Δee_P values of only few percent, and a hyperpositive NLE is clearly achieved only using substituents with $\sigma_P \approx 0$ (H, F, 2-naphtaldehyde), except for electron-donating -OiPr which also gives a hyperpositive NLE. Otherwise, there are no general trends to read from these results. -OMe again stands out as an exception, giving a much lower ee_P of ca. 50% with both 100 and 20% ee_L; -OCF₃ too, but only when using scalemic ligand (29% ee_P), same goes for -CN and -SF₅ in a less pronounced way (ca. 60% ee_P).

The fact that the reactions with ZnEt_2 show only small differences in ee_P between the different substrates, when compared their ZnMe_2 counterparts, may indicate that the dimeric catalyst plays a minor role with ZnEt_2 – either because of a low dimer/monomer ratio or because the monomer is significantly more active than the dimer. This is further supported by the overall high ee_P values obtained with ZnEt_2 , which also suggest a stronger participation of the monomeric catalyst. Another possible factor might be the increase of the catalysts' enantioselectivities ee_m and/or ee_d when switching from ZnMe_2 to ZnEt_2 . However in case of Noyori's system, the monomeric DAIB yields similar ee_P values with both dialkylzinc reagents (ZnEt_2 : 98% at 0 °C; ZnMe_2 : 95% at 40 °C).^{17,18} This indicates

that the nature of the alkyl group has only minor influence on the enantioselectivity of the catalytic step. Therefore, with NBE a significant change in enantioselectivity seems unlikely when switching from ZnMe_2 to ZnEt_2 , at least for the monomeric (-)-NBE- ZnMe complex.

FIGURE 4. Product ee of NBE-catalysed additions of a) ZnMe_2 and b) ZnEt_2 to *para*-substituted benzaldehydes using (-)-NBE with 100% (blue dots) or 20% ee_L (orange triangles). The results are sorted according to the substituent's σ_P values. Outliers (OMe, OCF₃, SF₅) are depicted by hollow dots and triangles. Each point is the mean of three different experiments; the vertical bars depict standard deviations.

In turn, it seems that the ZnMe_2 -system is more adapted for this study as the overall lower ee_P and higher Δee_P values indicate that both monomer and dimer participate significantly in the reaction. Therefore, possible changes in the catalytic system upon substrate variation are more likely to be observed with ZnMe_2 , and the remarkably low ee_P values yielded by electron-rich substrates might be caused by such a change. A decrease of ee_m and/or ee_d or a faster achiral background reaction (which may be accelerated by the coordinating -OMe and -OiPr groups) are possible but not sufficient to explain this behaviour, as the DAIB ligand gives only slightly lower ee_P with OMe-substituted benzaldehyde (88%) than with the unsubstituted one (95%).²⁰

Therefore, an increased dimer/monomer ratio or dimer/monomer relative reaction rate in presence of electron-rich substrates seems to be more likely to lower ee_P . It should be noted that the electron-rich substrates react only sluggishly and gave only low conversion values after 4 days (cf. Supporting Information for detailed conversion data). We have reported before that ee_P increases over time, at least in the early stage of the NBE-catalysed reaction with $ZnMe_2$.⁹ However, the low conversion cannot account alone for the low ee_P since certain electron-rich substrates do also reach only low conversions, although their ee_P stays high.

Conclusion

The study of dialkylzinc addition to benzaldehyde, catalysed by chiral (-)-NBE, has allowed us to find the first example of a hyperpositive NLE. This fulfils Kagan's 25 years-old prediction of a scalemic catalyst being able to be more enantioselective than its enantiopure counterpart, even though the mechanism turned out to be different from what Kagan proposed at that time. Instead of the ML_3 model, we have found (-)-NBE to follow a model in which both monomeric and homochiral dimeric (-)-NBE- ZnR ($R = Me, Et$) catalyse, the aggregate being less enantioselective than the discrete complex. Precipitation of an insoluble *meso*-aggregate allows to trap the minor enantiomer catalyst and to generate an enantioenriched monomer/dimer equilibrium that induces a hyperpositive NLE. Evidence for this model has been found by varying the catalyst loading, the reaction temperature, by DOSY NMR investigations and by kinetic analyses (catalyst order vs. catalyst loading and ee_P vs. time). Furthermore, we have started to study the influence of *para*-substituents on the benzaldehyde substrate on the overall catalytic outcome. Preliminary results suggest that electronic effects from the substituents may induce changes in the relative reaction parameters (dimer/monomer concentration ratio, dimer/monomer reaction rate ratio) and thus give information about the distinct monomeric and dimeric catalytic cycles. A more advanced study including the analysis of Hammett plots is underway.

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